

**PILOT CLINICAL TRIAL FOR THE EVALUATION OF TRANSCRANIAL ALTERNATING
CURRENT STIMULATION FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER**

IRB # 14-1622

NCT02339285

Funding Mechanism: National Alliance for Research on Schizophrenia and Depression
(NARSAD) - The Brain and Behavior Research Foundation

Principal Investigator: Dr. Flavio Frohlich, PhD

Co-Investigator: Dr. David Rubinow, MD

Draft or Version Number: 5.0

04 January 2016

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (May 9, 1997)

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Participants Protection and HIPAA Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Signed: _____ Date: _____

TABLE OF CONTENTS

	Page
Statement of Compliance	2
Signature Page	3
Table of Contents	4
List of Abbreviations	7
Protocol Summary	9
1 Key Roles	13
2 Introduction: Background Information and Scientific Rationale	15
2.1 Background Information	15
2.2 Rationale	15
2.3 Potential Risks and Benefits	16
2.3.1 Potential Risks	16
2.3.2 Known Potential Benefits	17
3 Objectives	19
3.1 Study Objectives	19
3.2 Study Outcome Measures	19
3.2.1 Primary Outcome Measures	19
3.2.2 Secondary Outcome Measures	19
4 Study Design	20
5 Study Enrollment and Withdrawal	21
5.1 Participant Inclusion Criteria	21
5.2 Participant Exclusion Criteria	21
5.3 Strategies for Recruitment and Retention	22
5.4 Treatment Assignment Procedures	23
5.4.1 Randomization Procedures	23
5.4.2 Reasons for Withdrawal	23
5.4.3 Handling of Withdrawals	23
5.4.4 Termination of Study	24
6 Study Intervention/Investigational Product	25
6.1 Study Product Description	25
6.1.1 Device Description	25
6.1.2 Operation	26
6.1.3 Safety Precautions	27
6.2 Preparation and Administration of Study Investigational Product	28
6.3 Assessment of Participant Compliance with Study Investigational Product	29
7 Study Schedule	30
7.1 Screening	30

7.2	Enrollment/Baseline.....	31
7.3	Stimulation Sessions.....	31
7.4	Follow-up.....	33
7.5	Final Study Visit.....	33
8	Study Procedures/Evaluations.....	34
8.1	Clinical Evaluations.....	34
8.2	Laboratory Evaluations.....	35
	8.2.1 Clinical Laboratory Evaluations.....	35
	8.2.2 Special Assays or Procedures.....	36
9	Assessment of Safety.....	37
9.1	Specification of Safety Parameters.....	37
9.2	Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters.....	37
	9.2.1 Adverse Events.....	37
	9.2.2 Expected Adverse Reactions.....	39
	9.2.3 Serious Adverse Events.....	39
	9.2.4 Unanticipated Problems.....	40
9.3	Reporting Procedures.....	40
	9.3.1 Reporting of Pregnancy.....	41
9.4	Type and Duration of Follow-up of Participants after Adverse Events.....	41
9.5	Halting Rules.....	41
9.6	Safety Oversight.....	42
10	Clinical Monitoring.....	43
10.1	Frohlich Lab Monitoring Plan.....	43
11	Statistical Considerations.....	44
11.1	Study Hypotheses.....	44
	11.1.1 Primary Objective.....	44
	11.1.2 Secondary Objective.....	44
11.2	Sample Size Considerations.....	44
11.3	Final Analysis Plan.....	44
12	Source Documents and Access to Source Data/Documents.....	45
13	Ethics/Protection of Human Participants.....	47
13.1	Ethical Standard.....	47
13.2	Institutional Review Board.....	47
13.3	Informed Consent Process.....	48
13.4	Exclusion of Women, Minorities, and Children (Special Populations).....	48
13.5	Participant Confidentiality.....	49
13.6	Study Discontinuation.....	49
14	Data Handling and Record Keeping.....	50
14.1	Data Management Responsibilities.....	50
14.2	Data Capture Methods.....	50

14.3	Types of Data	50
14.4	Timing/Reports	51
14.5	Study Records Retention.....	51
14.6	Protocol Deviations.....	52
15	Publication Policy	53
16	Literature References	54
	Supplements/Appendices	57
	<i>Appendix A: Schedule of Events.....</i>	<i>57</i>
	<i>Appendix B: Study Start Up Checklist</i>	<i>58</i>
	<i>Appendix C: Documentation of Informed Consent Process.....</i>	<i>59</i>
	<i>Appendix D: Consent Amendment Tracking Log.....</i>	<i>61</i>
	<i>Appendix E: Informed Consent Evaluation Feedback.....</i>	<i>62</i>
	<i>Appendix F: IRB Amendment Tracking Log.....</i>	<i>63</i>
	<i>Appendix G: Note to File.....</i>	<i>64</i>
	<i>Appendix H: Inclusion/Exclusion Criteria Checklist with signature of PI for participant eligibility.</i>	<i>65</i>
	<i>Appendix I: Telephone Contact Log.....</i>	<i>66</i>
	<i>Appendix J: Adverse Event Tracking Log</i>	<i>67</i>
	<i>Appendix K: Unexpected/Serious Adverse Event Tracking Log.....</i>	<i>68</i>
	<i>Appendix L: Adverse Event Report Form</i>	<i>69</i>
	<i>Appendix M: Serious Adverse Event Report Form.....</i>	<i>71</i>
	<i>Appendix N: Delegation of Authority Log</i>	<i>75</i>
	<i>Appendix O: Protocol Deviation</i>	<i>76</i>
	<i>Appendix Q: Enrollment Log.....</i>	<i>77</i>
	<i>Appendix R: Training Log</i>	<i>78</i>
	<i>Appendix S: Participant Off Study.....</i>	<i>79</i>
	<i>Appendix T: Telephone Recruitment Script.....</i>	<i>81</i>

LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
CAPA	Corrective and Preventative Action
CFR	Code of Federal Regulations
CGI	Clinical Global Interview
CNS	Central Nervous System
Co-I	Co-Investigator
CRF	Case Report Form
CRMS	Clinical Research Management System
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
dl-PFC	Dorso-lateral Prefrontal Cortex
DMV	Department of Motor Vehicles
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (Version IV)
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDRS17	Hamilton Depression Rating Scale (17 item)
HIPAA	Health Insurance Portability and Accountability Act
HSD	Honest Significant Difference
Hz	Hertz
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
JAMA	Journal of the American Medical Association
LAR	Legally Authorized Representative
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
MOCA	Montreal Cognitive Assessment
NAMI	National Alliance on Mental Illness
NARSAD	National Alliance for Research on Schizophrenia and Depression
NIH	National Institutes of Health
NIMH	National Institute of Mental Health

NRB	Neurosciences Research Building
OHRE	Office of Human Research Ethics
OHRP	Office for Human Research Protections
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SB	Suicidal Behavior
SI	Suicidal Ideation
SMC	Safety Monitoring Committee
SPI	Serial Peripheral Interface
SOP	Standard Operating Procedure
tACS	Transcranial Alternating Current Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
UE	Unexpected Event
UNC	University of North Carolina
UNC-CH	University of North Carolina at Chapel Hill
US	United States
YMRS	Young Mania Rating Scale

PROTOCOL SUMMARY

Title: Pilot Clinical Trial for the Evaluation of Transcranial Alternating Current Stimulation for the Treatment of Major Depressive Disorder

Précis: The purpose of this clinical trial is to investigate the effects of non-invasive transcranial alternating current stimulation (tACS) on patients who suffer from Major Depressive Disorder (MDD). We will recruit 60 males and females with unipolar, non-psychotic MDD. Eligible participants will have 5 daily (one week Monday through Friday), 40 minute stimulation sessions. Participants will be randomly assigned to one of three groups; sham stimulation, 10 Hz (alpha) tACS or 40 Hz (gamma) tACS. Participation will include 1 to 8 visits. At the initial session, consent will be given and eligibility will be determined. Eligible participants will undergo 5 daily stimulation sessions (40 minutes duration) with daily assessment of suicide risk, mania, and stimulation side-effects. Clinical assessments will be performed at baseline, 5th day of stimulation, the 2 week follow-up and the 4 week follow-up using the Montgomery-Asberg Depression Rating Scale (*Attachment 8*). Neurophysiological (EEG) and cognitive assays will be performed before and after stimulation. *Please see Appendix A for a detailed schematic describing all visits and assessments.*

Objectives: Our primary objective is to conduct a pilot clinical trial to establish the feasibility and collect first effectiveness data for the treatment of patients with MDD with tACS. The treatment rationale is to down-regulate pathological alpha oscillations in left dl-PFC of unmedicated patients with MDD. The primary outcome measure of this study is the change in Montgomery-Asberg Depression Rating Scale (MADRS) between initial assessment and assessment at the 4 week follow-up. In addition, we will also assess the change in MADRS between week 2 and week 5. Changes in alpha power between the first and the last day of stimulation is the secondary outcome of this study. In addition, we will perform explorative analysis of the EEG data

from all three time points as a pilot study for the future development of EEG-based biomarkers.

Population:	We will recruit 60 males and non-pregnant females ages 18-65 with a diagnosis of unipolar, non-psychotic MDD, who have been free of medication for the treatment of MDD for at least 6 months, including antipsychotic and anticonvulsant medications. Eligible participants will have a Hamilton Depression Rating Scale > 17 and low suicide risk. Participants will be recruited from the Chapel Hill, Durham and Raleigh areas.
Phase:	Pilot Study
Number of Sites:	This is a single site study performed at University of North Caroline- Chapel Hill.
Study Duration:	This study will take 2 years to complete
Participant Participation Duration:	Eligible participants who complete this clinical trial will have a total of 8 visits; an initial session, 5 days of stimulation, a 2 and a 4 week follow up visit (Follow up sessions are measured from first day of stimulation). The initial session will take approximately 2 hours, the first and last day of stimulation will take approximately 5 hours. Days 2 through 4 of stimulation will take 1.5 hours each day. The one week follow up will take approximately 2 hours and the four week follow up will take approximately 4 hours. We estimate that total participation to be approximately 22.5 hours.
Description of Agent or Intervention:	We will be using an active sham, 10 Hz and 40 Hz tACS. Active sham treatment will include 10 seconds of ramp in to 1 minute of 10 Hz tACS with a ramp out of 10 seconds for a total of 80 seconds of stimulation. The choice of an active sham is motivated to enhance success of patient blinding by mimicking skin sensations associated with tACS. Both 10 Hz and 40 Hz will also have a 10 second ramp in and ramp out with 40 minutes of stimulation for a total of 2420 seconds. Stimulation waveforms are sine-waves with a peak-to-peak amplitude of 2 mA. Participants will stay in a relaxed yet experimentally controlled state by watching a nature movie such as “Reefscape” during stimulation.

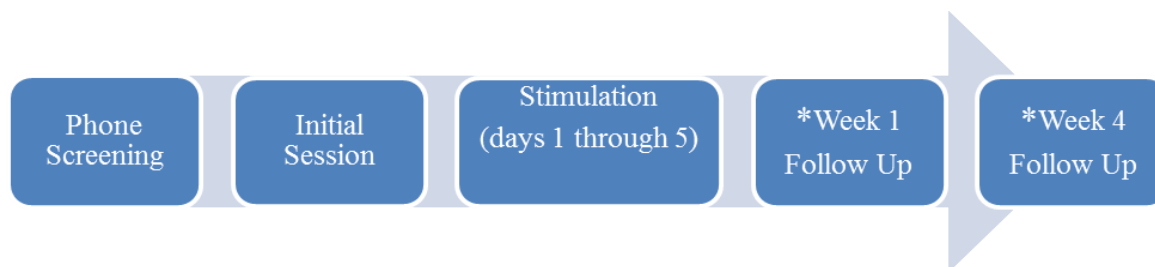
**Estimated Time to
Complete Enrollment:**

We estimate that it will take 2 years to complete enrollment of participants.

***Schematic of Study Design:**

Table 1. The 60 participants will be randomized into one of three of the following arms

ARM 1	20 participants	Sham
ARM 2	20 participants	10 Hz tACS
ARM 3	20 participants	40 Hz tACS



*Weeks are based on time from initial stimulation session

Initial Session	Day 1 of Stimulation (baseline)	Days 2 - 4 of Stimulation	Day 5 of Stimulation	Week 2 Follow Up	Week 4 Follow Up (endpoint)
<ul style="list-style-type: none"> • Obtain Consent -30 mins • MINI- 90 mins • HDRS17- 25 • Handedness-5 mins • Pregnancy test-5 mins • Demographics-1 min • Determine eligibility • Saliva collection for BDNF- 5 mins • 3.5 hours 	<ul style="list-style-type: none"> • Suicide Assessment - 1 min • YMRS- 25 mins • MOCA- 15mins • MADRS- 30 mins • HDRS17 - 30 mins • BDI- 5 mins • CGI - 1 mins • EEG- 60 mins • n-back working memory task - 20 mins • 40 minutes of active or sham treatment - 60 mins • Stimulation adverse effects Questionnaire - 5 mins • 6 hours 	<ul style="list-style-type: none"> • Suicide Assessment - 1 min • YMRS - 25 min • 40 minutes of active or sham treatment - 60 mins • Stimulation adverse effects Questionnaire - 5 mins • 1.5 hours 	<ul style="list-style-type: none"> • Suicide Assessment-1 min • YMRS- 25 mins • MADRS - 30 mins • HDRS17 - 30 mins • BDI- 5 mins • CGI - 1 mins • EEG-60 mins • n-back working memory task-20 mins • 40 minutes of active or sham treatment- 60 mins • Stimulation adverse effects Questionnaire- 5 mins • 6 hours 	<ul style="list-style-type: none"> • Suicide Assessment- 1 min • YMRS- 30 mins • MADRS - 30 mins • HDRS17 - 30 mins • BDI- 5 mins • CGI - 1 mins • 2 hours 	<ul style="list-style-type: none"> • Suicide Assessment - 1 min • YMRS 25 min • MADRS - 30 mins • HDRS17 - 30 mins • BDI- 5 mins • CGI - 1 mins • Symptom Improvement Questionnaire- 1 min • MOCA- 15 min • EEG 60 mins • n-back working memory task - 20 mins • 4.5 hours

1 KEY ROLES

Individuals:

Principal Investigator: Flavio Frohlich, Ph.D.

Co-Investigator: David Rubinow M.D.

Medical Monitor: Asa Cordle, M.D.

Flavio Frohlich Ph.D. – Principal Investigator
UNC - Chapel Hill Department of Psychiatry
Email: flavio_frohlich@med.unc.edu
Office: 4109F Neuroscience Research Building
Phone: (919) 966-4584

David Rubinow M.D. – Co-Investigator
UNC - Chapel Hill Department of Psychiatry
E-mail: drubinow@med.unc.edu
Office: 304 MacNider Hall
Phone: (919) 445-0208

Courtney Lugo MPH. – Project Manager/Study Coordinator
UNC - Chapel Hill Department of Psychiatry
E-mail: courtney_lugo@med.unc.edu
Office: Medical School Wing C-233
Phone: (919) 962-5271

Juliann Mellin B.A. – Study Coordinator
UNC - Chapel Hill Department of Psychiatry
E-mail: juliann_mellin@med.unc.edu
Office: Medical School Wing C-233
Phone: (919) 966-9929

Morgan Alexander B.S/BA – Study Coordinator
UNC_ Chapel Hill Department of Psychiatry
E-Mail: Morgan_Alexander@med.unc.edu
Office: Medical school Wing C- 233
Phone: (919) 966- 5271

Michael Boyle B.S. – Graduate Research Assistant
UNC - Chapel Hill Department of Biomedical Engineering
Email: mrboyle@live.unc.edu

Office: 4129 Neuroscience Research Building
Phone: (919)-966- 2682

Bradley Vaughn M.D. – Other
UNC - Chapel Hill Department of Neurology

E-mail: vaughnb@neurology.unc.edu
Office: 2122 Physician Office Building
Phone:(919) 966-8178

Asa Cordle M.D. – Medical Monitor
UNC - Chapel Hill Department of Psychiatry
Email: cordle@email.unc.edu
Office: UNC Hospitals CB# 7160
Phone: (919) 966-5217

Institutions:

University of North Carolina- Chapel Hill

Other:

IRB
University of North Carolina-Chapel Hill
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-311

Brain & Behavior Research Foundation
90 Park Avenue, 16th Floor
New York, NY 10016
(646) 681-4888

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Major depressive disorder (MDD) is a common, severe psychiatric illness that is associated with pathological dynamics of large-scale neuronal networks. More effective and safe therapies for MDD are desperately needed. Brain research has recently begun to uncover the biological substrate of depression: impaired ability of the brain to organize its electric activity into meaningful patterns that enable effective information processing.

Patients with MDD exhibit elevated oscillatory activity in left dorso-lateral prefrontal cortex (dl-PFC) in the alpha (8-12 Hz) frequency band (Henriques and Davidson, 1990). Alpha oscillations represent a fundamental state of neuronal hypoactivity that actively mediates suppression of information processing in thalamo-cortical circuits (Laufs et al., 2003; Palva and Palva, 2007). Transcranial magnetic stimulation to treat MDD has been recently approved by the FDA and is based on stimulation with a 10 Hz pattern. Importantly, bifrontal stimulation in the alpha frequency band with low-amplitude electric fields have recently been found to reduce symptoms in a multicenter, double-blind, sham-controlled study (personal communication, Dr. Linda Carpenter, Brown University). However, it has remained unknown if transcranial alternating current stimulation (tACS), a safe and non-invasive brain stimulation modality, is also an effective modulator of the network dynamics that mediate symptoms of depression. Addressing this lack in knowledge is critical for advancing our understanding of the network-level substrate of MDD and for the rational design of novel brain stimulation paradigms that directly target pathological network dynamics.

2.2 Rationale

Hypoactivity in the left dorso-lateral prefrontal cortex is a hallmark of MDD (Brunoni et al., 2010). Increasing activity levels by transcranial direct current stimulation (tDCS) that utilizes a constant current to increase cortical excitability has recently been demonstrated to be effective for the treatment of MDD (Brunoni et al., 2013). However, previous studies were more equivocal and recent meta-reviews came to differing conclusions (Berlim et al., 2013; Kalu et al., 2012). Our approach aims to use more targeted stimulation that directly modulates oscillatory activity. Specifically, we use non-invasive brain stimulation to target pathologically increased levels of alpha oscillations in left dl-PFC in depressed patients (e.g. Henriques and Davidson, 1990). tACS utilizes sine-wave stimulation waveforms that likely enhance specific oscillations (Ali et al., 2013; Herrmann et al., 2013). In contrast, suppressing oscillations with tACS, such as for the downregulation of pathologically enhanced alpha oscillations, is a more challenging task. The proposed work is the first study of its kind to evaluate the feasibility and effectiveness of two

different tACS-based stimulation paradigms. We will use 10 Hz stimulation motivated by the recent success in 10 Hz stimulation for treatment of depression with transcranial magnetic stimulation and we will use 40 Hz stimulation in order to indirectly modulate alpha oscillations due to endogenous antagonistic coupling of alpha and gamma frequency activity.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risk of Confidentiality Breach: In the unlikely event of a breach of confidentiality, people might discover that an individual was involved in this research study. This is especially sensitive because the clinical population recruited for this study may be subjected to negative consequences caused by the stigma of mental disorders. Furthermore, some might not agree with the principle of participating in research or of changing natural brain activity. To avoid breaches in confidentiality, study documents that contain personal information, including the informed consent document, and the document that links study ID numbers to personal identifying information are kept in locked filing cabinets in locked rooms, separate from any source documents containing participant dummy identifiers. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers, and data encryption methods will be used during communication between investigators. Only study personnel will have access to these data. All study staff participate in annual human participant training that includes education about responsibilities to the minimize risk of confidentiality breach.

Risk of Embarrassment: Self-report assessments contain questions regarding sensitive personal information. This risk is necessary in order to assess mood symptoms and associated psychopathology. Participants will be assured upon intake that only study personnel will see any clinical ratings.

Risk of Injury and Discomfort: Transcranial current stimulation has been used without any reports of serious side-effects for more than a decade. This stimulation mode has NOTHING to do with electroconvulsive therapy that applies many orders of magnitude higher stimulation current. Rather, transcranial current stimulation is so weak that it does not cause super-threshold activation of neurons (Frohlich and McCormick, 2010). In particular, tACS has been used without reports of any serious side-effects. Some participants report a transient mild tingling, burning, or itching underneath the electrodes and headache, but no other side effects have been noted. Importantly, it remains unclear if these mild side-effects were caused by the transcranial brain stimulation. In order to monitor these side-effects, we will be administering an adverse effects stimulation questionnaire (*Attachments 6 & 7*) after each stimulation session to determine whether

these effects were experienced. Research personnel present during these sessions will also check in with the participant periodically during the stimulation to see whether they are comfortable. If any side-effect occurs (rated by the participant as stronger than “moderate”) or the participant is experiencing severe discomfort, the stimulation will be immediately stopped.

There is a purely theoretical likelihood that stimulation of neuronal circuits can lead to epileptic discharges. To minimize this occurrence, we screen and exclude patients with personal and family history of neurological conditions from the study. If abnormalities or a seizure is witnessed during the course of the study, a referral will be made to the UNC Department of Neurology for follow-up. In the theoretical event that a seizure is witnessed that involves the loss of consciousness, the patient will be told not to operate a motor vehicle until cleared by the DMV.

Patients with MDD have an about 20 times higher rate of suicide than average. We have no evidence that our treatment paradigms will in any way increase this likelihood. Patients with high suicide risk will not be included in this study. If an enrolled patient shows signs of suicide risks that were not apparent during enrollment, a referral to UNC Psychiatry will be made. Dr. Rubinow, Co-I, will facilitate this process.

We will be using the Suicidality Module included in the M.I.N.I 7.0 to assess suicide risk. Inclusion criteria states that the patient must be low suicide risk, potential participants that have an above “low risk” designation will not be eligible for the study. We will administer a daily questionnaire to assess suicide risk. In the case suicide risk increases during participation in the study, the participant will be asked to stop the study and will be provided with a referral to UNC Department of Psychiatry and their mental health care or family medical doctor will be contacted.

2.3.2 Known Potential Benefits

Major depressive disorder is a common, severe psychiatric illness. Patients with MDD exhibit elevated oscillatory activity in left dorso-lateral prefrontal cortex. Our novel approach introduces non-invasive brain stimulation for mental illnesses and has the potential to treat symptoms not only in depression but also schizophrenia, and anxiety disorders.

This study has not been designed to benefit the individual participants. However, participants in this study may experience some degree of relief from mood symptoms as a result of tACS treatment. There are no serious risks to the participant from the treatment used in this study. The chance to understand and develop a new treatment

for a wide range of psychiatric disorders is an important step in helping the millions of people in the world who suffer from mental illness.

3 OBJECTIVES

3.1 Study Objectives

Our primary objective is to conduct a pilot clinical trial to establish feasibility and to collect first effectiveness data for the use of tACS to renormalize pathological alpha oscillations in dl-PFC of unmedicated patients with MDD by comparing MADRS scores from baseline and 5 week follow up visit.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The Montgomery-Asberg Depression Rating Scale (*Attachment 8*) will be the primary outcome measures for this study. This measurement will be taken at baseline (first day of stimulation), last day of stimulation, at the 2 week and at the 4 week follow up visits. We will compare the MADRS scores between baseline and 4 week follow up as our primary outcomes measure.

3.2.2 Secondary Outcome Measures

As a secondary outcomes measure, we will compare alpha oscillation power from resting state EEG recordings on the first and last day of stimulation. We will also collect EEG data at the 4 week follow up visit. We will use these data to analyze alpha frequency activity as a pilot study for derivation of EEG biomarkers.

4 STUDY DESIGN

The design for this study is a pilot, randomized, double blind, sham-controlled, clinical trial which will be used to demonstrate feasibility and collect effectiveness data for further refinement of a tACS approach and for the subsequent design of a follow-up, multi-site, large-scale study. We are recruiting from a clinical population. For this clinical trial we are seeking 60 males and non-pregnant females ages 18-65 with unipolar, non-psychotic MDD, free of benzodiazepine and anticonvulsant medication, who have a Hamilton Depression Rating Scale > 8 and are at a low risk for suicide according to the Hamilton Depression Rating Scale. All women of child-bearing potential will be asked to take a pregnancy test during the initial session in order to determine eligibility for the study. These individuals will be outpatients and may seek mental health care from a family practitioner, therapist or psychiatrist.

This is a single site, pilot clinical trial with 3 arms. We estimate 2 years to complete study enrollment.

Participants will be randomly assigned to one of three arms; active sham stimulation, 10 Hz (alpha) tACS or 40 Hz (gamma) tACS. Active sham treatment will include 10 seconds of ramp in to 1 minute of 10 Hz tACS with a ramp out of 10 seconds for a total of 80 seconds of total stimulation. The choice of an active sham is motivated to enhance success of patient blinding by mimicking skin sensations associated with tACS. 10 Hz and 40 Hz tACS will have a 10 second ramp in and ramp out with 40 minutes of stimulation for a total of 2420 seconds. Stimulation waveform is a sine-wave with a peak-to-peak amplitude of 2 mA. In each arm, participants will stay in a relaxed and yet controlled state by watching a nature movie such as “Reefscape” during stimulation.

Eligible participants who complete this clinical trial will have a total of 8 visits; an initial session, 5 days of stimulation, a 2 and a 4 week follow up visit. The initial session will take approximately 3 hours, the first and last day of stimulation will take approximately 6 hours and days 2 through 4 of stimulation will take 1.5 hours each. The one week follow up will take approximately 2 hours and the four week follow up will take approximately 4.5 hours. We estimate that total participant participation duration will be approximately 26 hours.

Our primary objective is to conduct a pilot clinical trial to establish the feasibility and to collect first effectiveness data for the use of tACS to renormalize pathological alpha oscillations in dl-PFC of unmedicated patients with MDD comparing MADRS scores from baseline to 4 week follow up visits. As a secondary objective we will assess the differential clinical effects of sham, 10 Hz and 40 Hz tACS on EEG measures of alpha oscillations.

5 Study Enrollment and Withdrawal

5.1 Participant Inclusion Criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- Provide signed and dated informed consent form
- Male or female, aged 18-65 years
- DSM-IV diagnosis of MDD; unipolar, non-psychotic
- Hamilton Depression Rating Scale score >8
- Capacity to understand all relevant risks and potential benefits of the study (informed consent)
- Meet criteria for low suicide risk
- Willing to comply with all study procedures and be available to do so for the duration of the study
- Women of reproductive potential must use highly effective contraception
- At least 6 months since their last ECT session

5.2 Participant Exclusion Criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- DSM-IV diagnosis of alcohol or substance abuse (other than nicotine) within the last month or a DSM-IV diagnosis of alcohol or substance dependence (other than nicotine) within the last 6 months
- Medical or neurological illness (unstable cardiac disease, AIDS, malignancy, liver or renal impairment) or treatment for a medical disorder that could interfere with study participation
- History of traumatic brain injury, reoccurring seizures or later cognitive rehabilitation, or causing cognitive sequelae
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips
- Co-morbid neurological condition (i.e. seizure disorder, brain tumor)
- Non English speakers
- Pregnancy, nursing, or if female and fertile, unwilling to use appropriate birth control measures during study participation
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study

- Current axis I mood, anxiety, or psychotic disorder other than major depressive disorder.
- Lifetime comorbid psychiatric bipolar or psychotic disorder.
- Eating disorder (current or within the past 6 months)
- Obsessive-compulsive disorder (lifetime)
- PTSD (current or within the last 6 months)
- ADHD (currently under treatment)
- Current use of benzodiazepines and/or antiepileptic drugs

5.3 Strategies for Recruitment and Retention

This clinical trial will utilize multiple recruitment strategies in order to communicate this opportunity to as many potential participants as possible. Our first means is through a referral process. Participants can be referred to the study through their primary mental health care provider or family doctor during routine visits. This type of recruitment will take place in doctors' offices throughout Chapel Hill, Carrboro, Durham and Raleigh areas. We estimate that approximately 20 participants will be enrolled from the Chapel Hill/Carrboro area and 10 between Durham and Raleigh. Clinicians will be informed of inclusion criteria through email and listserv announcements and be asked to mention this clinical trial to appropriate patients and offer them a flyer/ brochure with contact information. Interested individuals can then call or email the secure line/address in order to set up a phone prescreening.

We will also be posting ads in the local newspapers including, the Independent Weekly. In addition to newspapers we will have postings on websites such as ClinicalTrials.gov and NAMI. We will have contact information and a brief summary of the clinical trial posted on the Frohlich Lab Facebook and Twitter pages. These strategies will assist in recruiting medication free patients. Finally, with permission from Jennifer Rothman, the NIMH Outreach Partner for North Carolina, we will speak about our study and hand out fliers at NAMI Family to Family meetings. In addition to these recruitment strategies, we will also be utilizing advertisements through Facebook and Craigslist, and have information about our study with study coordinator contact information on Join the Conquest, ClinicalTrials.gov, and Studypages.com. Interested individuals need simply to read the information about the study and contact the study coordinator to complete the phone screening.

Our retention strategy includes a payment schedule of four times per participant. The participant will receive payment at the initial session, the 5th day of stimulation, and both follow up sessions, at the final follow up session will include a completion bonus of \$20.00. The research staff will also give each participant a reminder call for the initial session, the first day of stimulation, and each follow up session. Each research staff member will be easily available for the participants to contact via email or phone. The inclusion criteria state that each participant must be able to

understand all risks and benefits associated with this study. We will be asking each participant to answer questions about the consent form to determine that the study process and the duration of participation are completely understood by all participants. We will aim to have a specific research team member assigned to complete all sessions with the same participant. However we will not require the same researcher to be present during stimulation sessions 2 through 4. The study team will work hard at forming a professional relationship with the participant so they feel comfortable and willing to discuss what may be sensitive information. Retention will be quantified by the fraction of participants coming to each scheduled session (the data from each session will be scored and documented the day of the session). Participants will no longer be eligible to continue the study if they miss any stimulation session.

5.4 Treatment Assignment Procedures

Participants will be randomized into one of three arms. This is a double blind study, so neither the participant nor the researcher will know which treatment the participant is receiving, if any.

5.4.1 Randomization Procedures

Kristin Sellers will randomize 60 codes which will be used by the study coordinator and research assistants. These codes are directly linked to which treatment participants receive (sham, 10Hz tACS or 40 Hz tACS). Kristin Sellers has no other responsibility in the study other than providing these randomized codes.

5.4.2 Reasons for Withdrawal

A study participant will be discontinued from further participation if:

- A participant answers yes to any of the daily suicide questionnaires.
- A participant has a YMRS score greater than or equal to 12.
- The participant has missed any day of stimulation.
- Any clinical adverse event (AE), laboratory abnormality, intercurrent illness or other medical condition, or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).
- A participant wishes to withdraw from further participation for any reason.

5.4.3 Handling of Withdrawals

We will collect safety data on any participant discontinued because of an AE or SAE. In any case, every effort will be made to undertake protocol-specified safety follow-up procedures. If voluntary withdrawal occurs, the participant will be asked to continue scheduled evaluations and complete an end-of-study evaluation. If an AE has been reported, researchers will help the participant seek the medical care they need and a follow up will be performed by the PI and Co-I. In the case of an early withdrawal, the researcher will complete a Participant Off Study form to document the withdrawal reason (*Appendix S*).

5.4.4 Termination of Study

This study may be prematurely terminated if, in the opinion of the investigator, there is sufficient reasonable cause. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data those are not sufficiently complete and/or evaluable.
- Plans to modify suspend or discontinue the development of the study device.

The IRB will be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

6 STUDY INVESTIGATIONAL PRODUCT

6.1 Study Product Description

We will be using a transcranial current stimulator designed in the Frohlich Lab for investigational research purposes and the NeuroConn devices used in previous IRB approved studies. The device is not implanted and has not been designed for or being used to support or sustain human life. This device does not have a potential for serious risk to the health, safety, or welfare of the participant. There has never been an instance of serious side-effect reported due to use of transcranial brain stimulation. Previous studies in the Frohlich Lab that used comparable devices have always been classified as “non-significant risk” by the UNC IRB.

In addition, some participants will be stimulated with the commercial, CE-certified NeuroConn Plus stimulator (for purely logistic reasons of device availability). The use of this device in this study has previously received a NSR designation on initial review by the full UNC IRB. Both devices are electrically equivalent and provide the same stimulation. The NeuroConn device description is as follows:

The DC-STIMULATOR is a CE-certified medical device for conducting non-invasive transcranial direct-current stimulation (tDCS) in humans. DC stimulation is used in clinical practice and in the research of stroke, epilepsy, migraine, tinnitus, depression, multiple sclerosis, dementia and chronic headache. The DC-STIMULATOR is a micro-processor-controlled constant current source. It meets the highest safety standards thanks to (hardware- and software-based) multistage monitoring of the current path. By continuously monitoring electrode impedance it can detect insufficient contact with the skin and automatically terminate stimulation, maximising patient safety.

The device's alphanumeric display and the 4 touch keys allow various stimulation modes to be selected and stimulation parameters such as current strength, duration, fade-in and fade-out to be set.

DC-STIMULATOR features:

- 1 channel (anodal and cathodal stimulation possible)
- Adjustable current up to 5,000 μA *
- Adjustable application time up to 30 minutes *
- 2 standard modes - single (continuous stimulation) and - pulse (cyclical stimulation activation/deactivation) with fade in and fade out
- Customer-specific programs possible (optional)
- "Study mode" for blind processing of genuine and 'pseudo' stimulation (optional)
- External trigger input (optional)

6.1.1 Device Description

The device consists of the following main components/subsystems:

1. Tablet with user interface application (App)
2. Microprocessor
3. Function generator chip
4. Voltage controlled current source
5. Safety circuitry

First, the stimulation parameters are specified by the user through the app. The parameters are:

1. tDCS/tACS
2. Number of channels
3. Amplitude
4. Test duration
5. Frequency (for tACS)
6. Password.

Next, the parameters are sent via Bluetooth to the microprocessor. The microprocessor interprets these parameters, and programs the function generator chip accordingly. The function generator then creates the programmed waveform, which is ultimately a voltage signal. The voltage signal is applied to a voltage controlled current source, which generates the specified amount of current through an arbitrary load resistance.

6.1.2 Operation

- A. The desired current value is scaled to a register value and stored in the function generator.
- B. The value in the register determines the percent of full scale output current, generated by the function generator.
- C. The generated current waveform from the function generator is driven through a specified resistance. The resulting voltage drop is amplified by an instrumentation amplifier.
- D. The voltage waveform from the output of the instrumentation amplifier is applied to a voltage controlled current source.

Current Sensor Circuit

A $33.2\ \Omega$ sense resistor is placed in series with the stimulation electrodes on the high side. Since high-side current sensing is used, any short circuit of the electrode terminals to ground will be detected. The stimulation current flows through this resistor and generates a voltage. The voltage across this resistor is sensed and amplified by the AD628 difference amplifier. The gain of the difference amplifier is set to 9.9039. The current sensor voltage is then shifted before it is read by the microprocessor and the hardware overcurrent safety feature.

Voltage Sensor Circuit

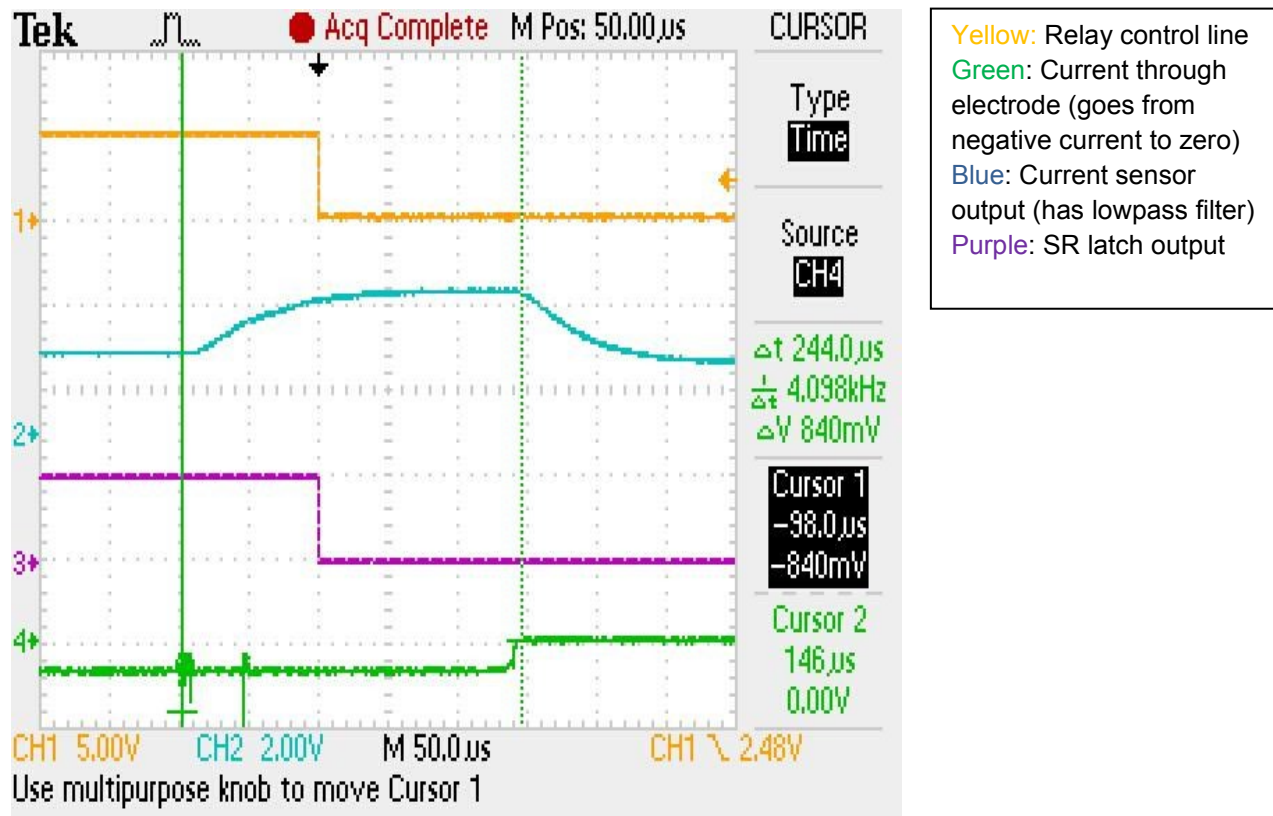
The differential voltage across the electrodes is measured so that the impedance can be calculated. The voltage is measured by buffering the positive electrode and negative electrode each with a unity gain op-amp circuit. The voltage sensor output is then shifted before it is read by the microprocessor using the same level shifting circuit described in the current sensor section.

6.1.3 Safety Precautions

The device is equipped with 4 different stages of safety protection, all of which protect the stimulant from high currents. The stages are as follows:

1. Automatic software current cutoff. The output of the current sensor described above is read by a microprocessor, which compares the reading to a value of $\pm 3\text{mA}$ peak. If the current exceeds these limits, stimulation is stopped, a relay in series with the electrode is opened, and the power supply used for stimulation is turned off. The user is then given the option to investigate the issue, and cancel or resume the test. Since high-side current sensing is used (described above), any short circuit of the electrode terminals to ground will be detected.
2. Automatic hardware current cutoff. The output of the current sensor is fed into a pair of comparators which detect if the current exceeds $\pm 4.5\text{mA}$. If so, the fault is latched such that the relay in series with the electrodes is opened. Additionally, the microprocessor is notified of this instance through an interrupt. Upon this interrupt, the microprocessor immediately stops stimulation and the power supply used for stimulation is turned off.

Figure 1: Example of successful hardware cutoff function



3. Permanent hardware current cutoff. A 5mA fast-acting fuse is in series with the electrode connector. If the above two over-current detection methods fail, the fuse will blow, and the stimulant will no longer be electrically connected to the device.

4. Power supply fuse. Finally, if for any other reason the entire device draws too much current, the main power supply fuse is blown. This fuse is sized with a cutoff of 200% of steady-state operating current.

6.2 Preparation and Administration of Study Investigational Product

After participants have completed the daily questionnaires, they will be comfortably seated. The research team will first measure their heads electrode placement using the 10-20 system. Participants will then be fitted with the 3 electrodes for stimulation. The participant will be in the relaxed yet, experimentally controlled state by watching a nature movie. One session of stimulation will be performed per day, for 40 minutes. In the 10 Hz and 40 Hz groups stimulation will have a 10 second ramp in and ramp out with 40 minutes of stimulation for a total of 2420 seconds. Stimulation waveforms are sine-waves with a peak-to-peak amplitude of 2 mA. The sham stimulation will include 10 seconds of ramp in to 1 minute of 10 Hz tACS with a

ramp out of 10 seconds for a total of 100 seconds of stimulation. Electrodes will be saline soaked, 5x5cm and placed over F3 and F4 with a 5x7cm placed over CZ as a return electrode.

Stimulation devices will be preprogrammed and codes will be randomized to one of the three experimental arms. Researchers will enter the participant-specific code into the App that controls the simulation and monitor participants during the 40 minutes of the stimulation.

The study coordinator and/or the research assistant will be thoroughly trained and have trainings documented on the transcranial stimulation device and will be present during all stimulation sessions. *Please see Appendix R for an example of the training documentation log.* To monitor side effects of stimulation a daily questionnaire will be administered after each stimulation session. *Please see Attachment 6 for an example of the daily stimulation questionnaire, and Attachment 7 for an example of the endpoint stimulation questionnaire.*

6.3 Assessment of Participant Compliance with Study Investigational Product

Compliance for this study includes making all 5 stimulation sessions. Follow up periods will be able to take place ± 3 days of scheduled visits.

7 STUDY SCHEDULE

Dr. Cordle or other approved clinician will be present during the 1st day of stimulation, the 5th day of stimulation, the 2 week and the 4 week follow ups to administer the CGI (*Attachment 3*) until research personnel are comfortable and certified to do so (will be determined by accompanying clinician). In order to increase data quality, the assessments for an individual participant at the initial session, the 1st day of stimulation, the 5th day of stimulation, the 2 week 4 week follow ups will be administered by the same researcher. Protocol for this study will not require the same researcher to be present during days 2 through 4 of stimulation although the team will strive to schedule the same researcher for every session.

7.1 Screening

Screening Telephone Call

Individuals who are referred by a mental health care provider will be contacted by a research for an initial phone screening. Researchers will keep a Telephone Contact log for each telephone conversation with a participant throughout the study. There will be a log for each participant and will be filed in the participant binder (*Appendix I*).

During the telephone screening, researchers will provide a brief background about MDD and tACS. Any initial questions will be answered at this point. The timeline of visits will then be explained; there will be 1 to 8 sessions, with 1 initial session, 5 consecutive week days of stimulation, 2 follow up sessions 2 weeks after the final stimulation and another 4 weeks after final stimulation. The participant will be informed that compensation for their participation will be received at 3 sessions throughout the study; the initial session, last day of stimulation, and at the 4 week follow up. The participant will be asked if they have any additional questions. Once all questions have been answered, the participant will be asked if he/she is still interesting in participating in the study. If yes, the researcher will begin the initial phone screening which will determine eligibility for the initial session. The screening questions are shown below. If the required answers are given for each question, the initial session will be scheduled and a reminder call will be given at least 24 hours before initial session. We will use the telephone script provided in *Appendix T* for all telephone screenings.

- Are you 18 years old or older? (Yes)
- Have you ever, or are you currently being treated for a neurological condition (i.e. epilepsy, migraines, etc)? (No)
- Are you currently taking medication for the treatment of depression or any other psychiatric illness? (No)
 - Have you ever taken medication for a mood disorder?
 - If yes, has it been at least 6 months since then?

- How long have you been depressed?
 - What steps have you taken to treat this depression?
 - Have you ever had brain surgery? (No)
 - Do you have any brain devices or implants, including a cochlear implant or aneurysm clip? (No)
 - Have you ever been diagnosed with a traumatic brain injury? (No)
 - For females only, is there a chance you may be pregnant? (No)
- Follow-up Questions
- Have you been diagnosed with Major Depressive Disorder by a professional (i.e. a psychiatrist or other licensed clinician)?
 - Have you ever been hospitalized?
 - If yes, was it in anyway related to a mood disorder or psychiatric condition?
 - If yes, when did this occur?

7.2 Enrollment/Baseline

Initial Session Visit (Visit 1, Day 0)

At the initial session participants will sign both a HIPAA authorization form and the consent form. Each form will be read to the participant by the researcher, and the participant will be given the time to ask any questions about the information discussed. Each participant will be asked a series of questions (Appendix E) to ensure that the consent form is fully understood.

Once consent is obtained, the researcher will verify that the participant meets inclusion criteria. If the participant is female, and unsure of pregnancy status, she will be asked to complete a urine pregnancy test to verify status. Next, demographic information will be collected, which will include a history of medication, alcohol, and drug use. This information is used to verify that the participant does not have an existing alcohol or drug dependency or disorder. A short handedness questionnaire will also be administered. Once the questionnaires and tasks are complete, the researchers will perform an 8 minute EEG recording. Participants will be asked to keep eyes open for 4 minutes and then keep eyes closed for 4 minutes during the recording. After the resting state EEG recording, the participant will be administered the “n-back” working memory task for a total of 20 minutes while a second EEG is being recorded. The n-back will be administered during each EEG recording following the resting state EEG. The following questionnaires will then be administered to further check eligibility; The Mini International Neuropsychiatric Interview (MINI) to confirm diagnosis and suicide risk, and the Hamilton Depression Rating Scale 17 item (HDRS17) will be used to assess the severity of depression (Attachment 5). At the end of the initial session, and once eligibility has been confirmed, a saliva sample will be collected (for testing of BDNF allele), the week of stimulation will be scheduled, and the participant will be paid.

7.3 Stimulation Sessions

Day 1 of Stimulation (Visit 2)

At the first day of stimulation, several questionnaires will be administered. First, the suicide assessment (*Attachment 4*), and YMRS (*Attachment 10*) will be administered to assess safety. These assessments will be administered at the beginning of each study visit. If the participant shows any development of SI, SB or manic symptoms, their participation will be stopped and their primary mental health care provider or family physician will be contacted. In the case that they do not see anyone for their depression, Dr. Cordle will assist the participant in seeking medical care.

Next, the HDRS17 (*Attachment 5*), MADRS (*Attachment 8*), BDI (*Attachment 1*), and CGI (*Attachment 3*) will be administered. These tools are used to collect information on the participant's symptom severity and are administered multiple times throughout the study. Baseline cognitive function tests will follow the symptom scale and include; the MOCA (*Attachment 9*) and the n-back working memory task.

Once the questionnaires and tasks are complete, the researchers will perform an 8 minute EEG recording. Participants will be asked to keep eyes open for 4 minutes and then keep eyes closed for 4 minutes during the recording. After the resting state EEG recording, the participant will be administered the “n-back” working memory task for a total of 20 minutes while a second EEG is being recorded. The n-back will be administered during each EEG recording following the resting state EEG. Then the participant will undergo either a sham, 10 Hz or 40Hz tACS treatment for 40 minutes. Participants will stay in a relaxed yet experimentally controlled state by watching a nature movie such as “Reefscape” during stimulation.

Finally, to assess any side effects of stimulation, the stimulation adverse effects questionnaire will be administered. This questionnaire will be administered at the end of each stimulation session (*Attachment 6*).

Days 2 – 4 of Stimulation (Visit 3 – 5)

The Suicide Assessment (*Attachment 4*) and the YMRS (*Attachment 10*) will continue to be administered at the beginning of each session. Once safety is assessed, and it is determined to be safe to continue, the participant will receive 40 minutes of sham, 10 Hz or 40Hz tACS (as per the initial randomization) while watching the assigned movie. The stimulation session will be followed by the stimulation adverse effects questionnaire ending the session. If the participant shows any development of SI, SB or manic symptoms, their participation will be stopped and their primary mental health care provider or family physician will be contacted. In the case that

they do not see anyone for their depression, Dr. Cordle will assist the participant in seeking medical care.

Day 5 of Stimulation (Visit 6)

The Suicide Assessment (*Attachment 4*) and the YMRS (*Attachment 10*) will be administered at the beginning of the session. Once safety is assessed and it is determined to be safe to continue, the participants will receive 40 minutes of either sham, 10 Hz or 40Hz tACS (as per the initial randomization) while watching the assigned movie, followed the stimulation adverse effects questionnaire. The HDRS17 (*Attachment 5*), MADRS (*Attachment 8*), BDI (*Attachment 1*), and CGI (*Attachment 3*) data collection assessments will be administered during this session. After the assessments are completed, an 8 minute EEG will be administered, with 4 minutes of eyes open and 4 minutes of eyes closed. Following this, the participant will perform the “n-back” working memory test for a total of 20 minutes. The participant will be paid at the end of this session for the completion of 5 stimulation sessions.

7.4 Follow-up

2 Week Follow-up Visit (Visit 7, 2 weeks after final day of stimulation)

The Suicide Assessment (*Attachment 4*) and the YMRS (*Attachment 10*) will be administered at the beginning of this session. The HDRS17 (*Attachment 5*), MADRS (*Attachment 8*), BDI (*Attachment 1*), and CGI (*Attachment 3*) assessments will be administered after safety has been assessed.

7.5 Final Study Visit

4 Week Follow-up Visit (Visit 8, 3 weeks after first follow up visit)

The Suicide Assessment (*Attachment 4*) and the YMRS (*Attachment 10*) will be administered at the beginning of this session. The participant will be asked to recall their experience of stimulation and answer the final stimulation adverse effects questionnaire (*Attachment 7*). This questionnaire will ask the participant whether they believed they received treatment (answer options include yes, no, and I don’t know) and whether they think their symptoms have improved. The HDRS17 (*Attachment 5*), MADRS (*Attachment 8*), BDI (*Attachment 1*), and CGI (*Attachment 3*) assessments will be administered, followed by the MOCA (*Attachment 9*) and n-back working memory task. After the cognitive assessments, a final 10 minute EEG will be administered, with 5 minutes of eyes open and 5 minutes of eyes closed. The participant will be paid at the end of this session including the study completion bonus.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

During the initial session, researchers will collect demographics. Participant demographics include medical history and medication history. This information is used to confirm inclusion criteria; CNS medications free for at least 6 months, and no current alcohol and drug abuses or disorder exist.

Several clinical evaluations will be used throughout this study. These assessments are listed below and can be found in the attached documents.

- i. The Mini International Neuropsychiatric Interview (MINI) is a short, structured interview that will be used during the initial session to confirm diagnosis of MDD, unipolar and non-psychotic with a low suicide risk. This scale has been validated as being a reliable diagnostic tool (Sheehan et al. 1998).
- ii. The Hamilton Depression Rating Scale 17-item (HDRS17) (Williams 2001; Khan et al 2002; Leentjens et al. 2000) will be administered during the initial session, day 1 of stimulation (baseline), day 5 of stimulation and at the 3 and 5 week follow ups. This scale is used to determine patient eligibility and to monitor the severity of the participant's depression symptoms. (*Attachment 5*)
- iii. The Beck Depression Inventory (BDI) (Beck et al. 1988; Dozois et al. 1998) will be administered at baseline, day 5 of stimulation and at week 3 and 5 follow up. The BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression and will be used to monitor the severity of the patient's depression throughout the study. (*Attachment 1*)
- iv. The Clinical Global Impression scale (CGI) (Khan et al. 2001) will be administered at baseline, day 5 of stimulation and at week 3 and 5 follow up. The CGI will be used to monitor the severity of the patient's symptoms and also as a measure of treatment response and efficacy. Dr. Cordle or other approved clinician will be present during the 1st day of stimulation, the 5th day of stimulation, the 2 week follow up and the 4 week follow up to administer the CGI until research personnel are comfortable and certified to do so. (*Attachment 3*)
- v. The Montgomery-Asberg Depression Rating Scale (MADRS) (Khan et al. 2001; Leentjens et al. 2001) will be administered at baseline, day 5 of stimulation and at week 3 and 5 follow up. This scale will be used as a primary outcome of this study and will be used to measure

the severity of depressive episodes experienced by participants. (*Attachment 8*)

We will be monitoring the safety of our participants throughout the study with the following assessments. These assessments can also be found in attachments.

- i. A suicide questionnaire previously used in IRB # 14-0600 will be used at each session of this study. This questionnaire tracks suicidal ideation and behavior. Participants will be asked to answer whether they have had any thoughts of hurting themselves within the past 24 hours and whether they have hurt themselves within the past 24 hours. If a participant admits to experiencing either SI or SB their participation will be stopped immediately and their primary mental health care provider or family physician will be contacted. In the case that they do not see anyone for their depression, Dr. Cordle will assist the participant in seeking medical care. (*Attachment 4*)
- ii. A stimulation adverse effects questionnaire will be administered at the end of each stimulation session and at the 5 week follow visit. This questionnaire will be used as a safety measure and to collect data on participant experience. A similar questionnaire was used in IRB 13-2995 to determine ability to successfully blind using transcranial current stimulation. (*Attachment 6 and Attachment 7*)
- iii. The Young Mania Rating Scale (YMRS) (Young et al. 1978) was designed to assess the severity of manic symptoms at baseline, with the ability to reassess the individual's symptoms over time. When undergoing treatment for depression, a possible effect of treatment is to alter the serotonin levels, potentially causing a manic episode. Although we do not expect such an event to occur since we are not using a medication that targets serotonin levels, we will be conducting this assessment at each evaluation as a precautionary measure. In the case a participant develops any sign of mania their participation in the study will be stopped and their primary mental health care provider or family physician will be contacted. In the case that they do not see anyone for their depression, Dr. Cordle will assist the participant in seeking medical care. (*Attachment 10*)

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

During the initial session, a urine pregnancy test will be performed for any female participant who is unable to confirm pregnancy status. This information will be recorded on the inclusion/exclusion criteria checklist (*Appendix H*) to be completed by the researcher.

8.2.2 Special Assays or Procedures

Two cognitive assays will be administered in order to assess cognitive abilities at baseline and again at the study endpoint. The Montreal Cognitive Assessment (MOCA) (*Attachment 9*) will be used to monitor changes in cognition since it has been developed to detect changes in cognition. In addition, an *n*-back working memory task will be administered during each EEG recording. This task is designed to detect changes in working memory performance that has been associated with overall functional integrity of neuronal circuits in the prefrontal cortex.

There will be two procedures used throughout this study. Each participant will attend 5 consecutive weekdays of stimulation for this study. Each participant will be randomly assigned to one of three treatment arms for this study (sham, 10HZ active tACS or 40 Hz active tACS). Electrodes with measurement 5x5cm will be placed over F3 and F4, and a return electrode, 5x7cm, will be placed over Cz. In order to detect any change(s) at the neurophysiological level, an EEG will be performed during the 1st day of stimulation, the 5th day of stimulation, and at the 5 week follow up session. This measurement will contribute to the design of novel network-level biomarkers of MDD and of treatment response.

In addition to the above procedures, we will be collecting a saliva sample at the initial visit. This sample will be used to test for a single nucleotide polymorphism in the BDNF gene whose presence may have an influence on effectiveness of brain stimulation. Within the central nervous system, BDNF regulates survival, proliferation, and synaptic growth as well as directly influences synaptic plasticity in the adult human brain (Antal et al. 2010). Egan et al. (2003) demonstrated that Val66Met, a single nucleotide polymorphism in the BDNF gene, has functional consequences in healthy humans including decreased episodic memory and hippocampal inducing a reduction in recall capacity. This polymorphism is common in over one third of the Caucasian population (65% Val66Val to 35% Val66MET) (Pezawas et al. 2004; Hariri and Weinberger 2003). Kleim et al. (2006) found that individuals with the Val/Val polymorphism respond to tDCS and transcranial magnetic stimulation treatments (TMS) with expected changes whereas individuals expressing the Val/MET allele do not. These authors indicate the difference to be caused by the impairment in synaptic plasticity caused by the Val/MET allele. These findings suggest that individual efficacy of treatments using brain stimulation may be partially genetically predetermined and should be taken into account when performing such procedures. Accordingly, we will conduct genotyping of all participants in this study in order to assess BDNF status. We will perform exploratory analyses in which we group participants by BDNF status.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

There will be three different assessments used to ensure participant safety. First, the Suicide Assessment (*Attachment 4*) will be administered at the beginning of each session. This assessment is used to determine SI and SB within the past 24 hours. If the participant answers “Yes” to either question, participation in the study will be stopped and their primary mental health care provider or family physician will be contacted. In the case that they do not see anyone for their depression, Dr. Cordle will assist the participant in seeking medical care.

Immediately following the Suicide Assessment, the YMRS (*Attachment 10*) will be administered. This assessment is used to detect any emergence of manic symptoms. If any manic symptoms become apparent, participation in the study will be stopped and their primary mental health care provider or family physician will be contacted. In the case that they do not see anyone for their depression, Dr. Cordle will assist the participant in seeking medical care.

After each stimulation session, a stimulation adverse effects questionnaire (*Attachment 6*) will be administered. This tool is used to document any side effects experienced during stimulation. The researcher will also check with the participant throughout the 40 minute stimulation sessions to make certain no discomfort is felt. The stimulation session will be terminated if the participant reports having unmanageable discomfort or pain (more than “moderate”). Additionally, this information will be reported on an AE report form (*Appendix L*) and an AE log (*Appendix J*).

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

Adverse Event: An AE, as defined by the NIH, is any unfavorable changes in health, including /abnormal laboratory findings that occur in trial participants during the clinical trial or within a specified period following the trial.

All AEs including local and systemic reactions not meeting the criteria for “serious adverse events” will be captured on the appropriate CRF. In addition, the AE Report Form will be completed by the study coordinator (*Appendix L*). The AE report form includes the follow; what is known about the therapy and previous reported side effects, if the AE occurred in temporal relation to the therapy, whether or not the AE improves or disappears when treatment is stopped, whether the AE is a worsening of baseline symptoms or related to a concurrent medical condition or medication use. Once complete,

this form will be given to the PI and the Co-I who will review, comment and sign this form. Completed forms will be placed in the participant's folder.

The study coordinator will document any AE occurrence on the AE log (*Appendix J*) which includes information such as the date of the AE, severity, relationship to the treatment (assessed by the PI), actions taken, and outcome(s). The log will be reviewed and initialed by the PI 72 hours after being completed. All AEs occurring during the clinical trial will be documented appropriately regardless of relationship to tACS. All AEs will be followed to adequate resolution and will be graded for severity and relationship to the study treatment. Any medical condition noted at the initial session will be considered as baseline and not reported as an AE.

All AEs will be graded for severity using the following guidelines.

- **Asymptomatic:** the participant is exhibiting no symptoms due to the event; no treatment needed.
- **Mild** Adverse Event– Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
- **Moderate** Adverse Event – Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication). In the case of a moderate adverse event the medical advisor may recommend an over the counter medication.
- **Severe and undesirable** Adverse Event – Event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

Changes in the severity of an AE will be documented with the Note to File document (*Appendix G*) and will be filed in the participant's folder.

Relationship to Study Products: The PI and Co-I will together determine whether an AE is associated with the study treatment. The event will be labeled associated if the event is temporally related to the administration of the therapy and no other factors can explain the event. The event will be labeled as not associated if the event is temporally independent of the study treatment and can be explained by external factors such as major life events.

9.2.2 Expected Adverse Reactions

Transcranial current stimulation has been used without reports of any serious side-effects. Some subjects report a transient mild tingling, burning, or itching underneath the electrodes and headache, but no other side effects have been noted. Importantly, it remains unclear if these mild side effects were caused by the transcranial brain stimulation. During the stimulation, the researcher will ask the participant about their comfort. Stimulation will immediately be stopped if any discomfort (more than “moderate”) is reported. In theory, there is a possibility that application of weak stimulation current could induce a seizure.

These adverse reactions will be monitored with the stimulation adverse effects questionnaire (*Attachment 6*). The following scale reflects the scoring of severity for any possible side effects.

- 1 = Absence of the indicated symptom
- 2 = Mild (awareness of a symptom but the symptom is easily tolerated)
- 3 = Moderate (discomfort enough to cause the researcher to be informed)
- 4 = Severe (incapacitating; the stimulation is terminated due to extreme discomfort)

All expected adverse reactions questionnaires are a daily source document that will be placed in each individual’s folder. Additionally, this data is imported directly into the RECap secure data base. Should the DSMB ask to see a complete report of this information we can generate a report using REDCap.

9.2.3 Serious Adverse Events

Serious Adverse Event (SAE): An SAE, as defined by the NIH, consists of adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant’s health is at risk and intervention is required to prevent an outcome mentioned.

All SAEs will be recorded on the Serious Adverse Events Form (*Appendix M*), documented in the UE/SAE log and reported to the IRB. The SAE Form will be completed by the study coordinator, and includes information relating to the onset and nature of the SAE, relationship to the study treatment, seriousness of the SAE, treatment required as a response to the SAE, and outcome. This form will be filed in the

participant's binder at the resolution of the event. The study coordinator will complete the UE/SAE log (*Appendix K*) which includes information such as the date of the event, time at which the study team was informed of the event, details, when the IRB has been notified, and the date that the SAE Form was completed.

9.2.4 Unanticipated Problems.

Unexpected Events (UE) will be recorded on the UE/SAE log (*Appendix K*) and will include information such as the date of the event, when the study team was informed of this event, details of the event, when the IRB was notified, and whether the SAE Form was completed. The IRB will be notified of each UE that may occur during the study.

The Office for Human Research Protections considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If an UE occurs the IRB will be notified and the study will be adjusted as needed to protect the health and safety of the participants. Depending on the nature of the UE, the research protocol, inclusion/exclusion criteria, and informed consent will be changed to reflect the possibility of this event reoccurring. *Please see Appendix D for an example of the Consent Amendment Tracking log.* During this time, no new participants will be recruited and the research procedures for currently enrolled participants will be stopped. Each UE will be recorded and reported throughout the study.

9.3 Reporting Procedures

We will be adopting the follow table for reporting procedures:

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported

Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 24 hours of initial receipt of information	Investigator	<ul style="list-style-type: none"> Local/internal IRBs
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within 48 hours of initial receipt of information	Study Coordinator	<ul style="list-style-type: none"> Local/internal IRBs/Institutional Officials, DSMB
Unanticipated adverse device effects	Within 10 working days of investigator first learning of effect	Investigator	<ul style="list-style-type: none"> Local/internal IRBs
Unanticipated Problem that is not an SAE	Within 7 days of the investigator becoming aware of the problem	Investigator	<ul style="list-style-type: none"> Local/internal IRBs/Institutional Officials,
All Unanticipated Problems	Within 30 days of the IRB's receipt of the report of the UP from the investigator.	IRB	<ul style="list-style-type: none"> OHRP
		Investigator ³	<ul style="list-style-type: none"> External IRBs

9.3.1 Reporting of Pregnancy

Pregnancy tests will be administered at the initial session to all women of child-bearing potential. There are no studies that suggest tACS would interfere with pregnancy. However, should a participant become pregnant during the study their participation will be immediately terminated and will be sent to consult with Co-I and medical monitor.

9.4 Type and Duration of Follow-up of Participants after Adverse Events

Medical monitors and Co-I will follow up with participants within one week of an AE.

9.5 Halting Rules

If a seizure occurs at the time of a study visit, a temporary hold will be placed over the study and further investigation will ensue. This could lead to stopping the study prematurely or continuing on with further safety measures in place. If two seizures are witnessed during the study visits, the entire study will be stopped prematurely. These individuals would be referred for further medical attention. It is very unlikely that a seizure will occur, given that previous studies using tDCS in patients with depression and schizophrenia have had no seizures occur (Berlin et al., 2013, Brunelin et al., 2012). The study will also be stopped (at least temporarily) if studies provide evidence that transcranial current stimulation caused brain damage or other harmful effects on

subjects, either short-term or long-term.

9.6 Safety Oversight

Safety oversight will be under the direction of a DSMB composed of Dr. Ross Simpson, an epidemiologist, a biostatistician and one or more clinical researchers. The DSMB will review AEs every 6 months whereas the medical monitor will review AEs in real time and make decisions as of participant's continuation of the clinical trial. The PI will review AEs weekly with research team and may request additional review by Co-I on a case-by-case basis. The medical monitor will also be present at weekly meetings in order to discuss/explain any event(s) that may occur.

Every 6 months DSMB will review blinded AE reports, scores from suicide questionnaires and any cognitive changes. If there is reason to view unblinded information, the DSMB will directly receive the list of participants' identification numbers from Kristin Sellers. Participant identification number will be displayed in a table according to the three arms of the study; however the specific treatment of that arm will not be disclosed. This will allow the DSMB to compare the three treatment groups.

Reasons for stopping the study and asking for further investigation include; increased suicide risk due to treatment (>25% of participants asked to seek mental health care), decrease in cognitive abilities based on baseline and end of study data (>25% decrease in scores in >15% of participants). In addition, as mentioned above, if a seizure occurs during a study visit, the clinical trial will be temporarily be placed on hold for further investigation.

10 CLINICAL MONITORING

The Purpose of the monitoring plan is to present the Frohlich Lab's approach to monitoring clinical trials. The plan facilitates compliance with good clinical practice.

- (a) The rights and well-being of human subjects are protected.
- (b) The reported trial data are accurate, complete, and verifiable from source documents.
- (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

This section identifies key monitoring activities and specifies the data to be reviewed over the course of a clinical trial. This is a single site, investigator initiated, clinical trial so there will be no site monitoring plan in place.

10.1 Frohlich Lab Monitoring Plan

The latest version of the approved IRB application for this clinical trial will be followed at all times. This responsibility falls in the hands of the study coordinator and research assistants. If at any time there is a deviation from protocol, the deviation from protocol log (*Appendix O*) will be filled out. All team members will be trained on how and when to use this log. The most up to date IRB application will be on file at the Clinical Trials desk in Rm 4109 of the NRB. Deviations will be sent to IRB every 4-6 weeks (if necessary).

At the end of the month clinical trials meeting with the PI, 3 randomly selected informed consent forms will be chosen. The PI will verify that (1) these forms have been filled out appropriately, and (2) the consent form process described in the SOP was followed and properly documented. Should any consent form be in violation, the research team will perform and document a complete review of all consent forms.

AE and SAE are clearly defined in the Master Protocol. Documents of AE and SAE can be found in the study binder on file at the Clinical Trials desk in Rm 4109 of the NRB. It is responsibility of the study coordinator to report all events to the PI. In all weekly meetings with the PI, all AE and SAE are discussed. For our practices we have adapted the decision tree provided by UNC-CH IRB to assist with reporting of such events (*Attachment I*).

At all weekly clinical trial team meetings, the study coordinator will chose one CRF and Source Document to assess for completion and maintenance. At weekly clinical trials meeting, with the PI will assess completeness of data on REDCap (data site). The PI has read-only access. This allows the PI to view reports that provide information on any missing data on an individual participant basis, but does not allow them to add, change or input any data.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

11.1.1 Primary Objective

Null hypothesis: There is no difference baseline and the 4 week follow up in MADRS score between treatment groups.

Alternative hypothesis: There is a difference between baseline and the 4 week follow up MADRS score between treatment groups.

11.1.2 Secondary Objective

Null hypothesis: There is no difference in changes of alpha frequency power between baseline EEG and EEG at completion of stimulation between treatment groups.

Alternative hypothesis: There is a difference in changes of alpha frequency power between baseline EEG and EEG at completion of stimulation between treatment groups.

11.2 Sample Size Considerations

This clinical trial represents a pilot study. A pilot study is a clinical trial that is conducted to decide whether a new treatment should be tested in a large controlled trial therefore we do not calculate sample size. It is difficult to recruit a large number of patients diagnosed with MDD to participate in a single site extensive study. However, we expect with 20 participants in each group that we have enough power to detect significance if there is a clear effect of tACS on depression and/or the underlying biomarkers.

11.3 Final Analysis Plan

We will perform spectral analysis of resting state EEG before and after stimulation treatment and use a mixed ANOVA with the within subject factor session (day one of stimulation and 4 week follow up) and between subject factor treatment (sham, 10Hz tACS or 40Hz tACS). Spectral analysis will be performed with multi-tapered estimation of the frequency spectrum followed by integration over the classical alpha EEG band (8-12 Hz). We will apply the same statistical analysis procedure for our primary outcome of MADR scale.

We will also use post-hoc paired or unpaired Student's t-test to identify the group or groups that differed. We will further control for multiple comparisons by using Bonferroni corrections.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Partners Human Research Committee (IRB):

- All IRB Correspondences are on file.
- The study staff is IRB approved prior to performing any study procedures.
- Adverse events and deviations are reported to IRB per current guidelines.
- All versions of the IRB protocols and informed consent forms are on file.

Informed Consent:

- Ensure that participant identification is on all pages of the ICF
- There is documentation that the participant is given a copy of the consent form (*Appendix C*)
- The participant and study representative signed and dated the consent form for him/herself.
- The participant initialed and dated all appropriate pages on the informed consent form.
- Note to file (*Appendix G*) made for any informed consent deviations.
- Ensure a valid (current version date) copy of the consent form was used.

Protocol:

- Confirm that the study staff is conducting the study in compliance with the protocol approved by IRB
- The protocol deviations (exceptions and violations) are documented in the participant chart and reported to IRB as required.

Source Documents:

- Each participant binder will contain a checklist to ensure that each binder has each source document. The checklist will be dated by the researcher for each time an assessment is administered. (*Appendix P*)
- Review participant charts to ensure the accuracy, completeness and legibility of the data
- Any correction made to the source documents is dated, initialed, and explained. The original entry should not be obscured.
- The protocol specific source documents are on file.
- Source documents are completed in ink.
- Note to files (*Appendix G*) are made for missing or incomplete data and to explain any discrepancies or additional comments.

Electronic Case Report Forms (eCRF)

- Ensure the data reported on the eCRF is consistent with the source documents.
- Discrepancies between the source documents and eCRF are explained in a note to file (*Appendix G*) or captured in a comment in the eCRF.

DNA

- Participant names will not be on any of the samples collected at the initial session. DNA testing is performed within the University of North Carolina at Chapel Hill and the samples are not shared with or processed by any third party outside the university.

The research coordinator, research assistants, and PI will have access to all of the above information. CO-I and medical monitor will have access to files upon request as they will need access to the locked rooms and filing cabinets in which these documents are located. The key linking dummy identifiers with subject information will be securely destroyed after completion of data acquisition.

13 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

13.2 Institutional Review Board

The Office of Human Research Ethics is responsible for ethical and regulatory oversight of research at UNC-Chapel Hill that involves human participants. The OHRE administers, supports, and guides the work of the Institutional Review Boards and all related activities. Any research involving human participants proposed by faculty, staff, or students must be reviewed and approved by an IRB before research may begin, and before related grants may be funded. OHRE and the IRBs are critical components of the coordinated Human Research Protection Program, which serves to protect the rights and welfare of human participants. All components of this program must work together to ensure institutional compliance with ethical principles and regulatory requirements. The following is a mission statement for the coordinated Human Research Protection Program:

The University of North Carolina at Chapel Hill is committed to expanding and disseminating knowledge for the benefit of the people of North Carolina and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research participants. Human participants are partners in research and a precious resource to the university. At UNC-Chapel Hill, human participant research is a privilege, but not a right. Consistent with that philosophy, it is the mission of the UNC-Chapel Hill Human Research Protection Program to ensure that

1. The rights and welfare of human participants are paramount in the research process;
2. The highest standards of ethical conduct are employed in all research involving human participants;
3. Research investigators are properly trained in the ethical and regulatory aspects of research with human participants;
4. Research investigators deal honestly and fairly with human participants, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and

5. Research using human participants at UNC-Chapel Hill conforms to all applicable local, state, and federal laws and regulations and the policies of the university.

13.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of tACS will be provided to the participants and their families. Consent forms describing, in detail, the study intervention, device, procedures, and risks are given to the participant and written documentation of informed consent is required prior to the administration of any treatment or assessments used in this study. *Please see Appendix C for an example of the Documentation of Informed Consent Process form.* All consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study (*Appendix D*).

Together, the researcher and potential participants will review the clinical trial in its entirety. At several intervals during the consent review, the researcher will ask the participant questions that will assess the comprehension of the information in the consent. If the participant is unsure or does not know, the researcher will return to that section and more carefully explain the information. Participants must sign the informed consent document prior to any procedures taking place. If needed, the participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 Exclusion of Women, Minorities, and Children (Special Populations)

Non-English speaking individuals are excluded because the ability to accurately and completely communicate study information, answer questions about the study, and obtain consent is necessary. Female participants will be asked if there is any reason to believe they might be pregnant. Pregnant participants will be excluded despite the fact that theoretical risk to mother or fetus is exceedingly small, since no safety data for pregnancy is known to exist for transcranial current stimulation studies. All women of child-bearing potential will be asked to take a pregnancy test during the initial session in order to determine eligibility for the study.

13.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the research team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

All data will only be referenced by dummy identifier code. Data will be stored on a password protected computer. A key connecting names and code numbers will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel. Participants will not be identified in any report or publication about this study.

13.6 Study Discontinuation

In the event that the study is discontinued, participants who have completed or who are still enrolled in the study will be notified. Any new information gained during the course of the study that might affect participant's willingness to continue will be communicated within 2 days of the PI learning this information.

14 DATA HANDLING AND RECORD KEEPING

The study coordinator and research assistants are responsible for the accuracy, completeness, legibility, and timeliness of the data reported. During weekly meetings, the data will be reviewed by the PI to check for completeness and continued safety of the participants and research staff. Any changes made to the data will involve crossing out the original data, documenting the new data with the initials and date of the researcher making the change.

14.1 Data Management Responsibilities

The responsibilities designated to each member of the research team are documented on the Delegation of Authority SOP (*Appendix N*). The study coordinator and research assistants will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, EEG administration, and CRF entries. The study coordinator will be responsible for AE/SAE documentation and reporting, while the PI will be responsible for the AE assessment, review of the AE documentation forms and overview of the research staff. Dr. Asa Cordle will be the medical monitor for the study.

REDCap will serve as a secure data management tool for this study. The study coordinator and research assistants will have complete access to the REDCap system, while the PI and Co-I will have read only ability. This will enable the researchers to enter the data and the PI and Co-I to review.

14.2 Data Capture Methods

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a data capture system provided by REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.3 Types of Data

Data will be collected to determine eligibility. During the initial session, the MINI, and the HDRS17 will be administered. In order to participate in this study, the participant must have a diagnosis of MDD (unipolar, non-psychotic), have a low suicide risk, and have a score of greater than 8 on the HDRS.

We will also be collecting data to assess cognitive abilities at baseline and endpoint (5 week follow up). The MOCA and *n*-back working memory task will be administered as two separate

measurements of cognition.

The Suicide Assessment and the YMRS will be administered at the beginning of each session to monitor the safety of the participant. The Suicide Assessment will be administered in order to evaluate whether the participant has experienced any SI or SB in the past 24 hours. The YMRS will assess the development of any manic symptoms throughout the study. The stimulation adverse effects questionnaire will be administered after each stimulation session in order to monitor any side effects the participant may experience from the stimulation treatment.

The MADRS will be our primary outcome for this study. We will administer this questionnaire on the 1st day of stimulation, the 5th day of stimulation, and the 2 and 4 week follow up. As our primary outcome, the data we collect with the MADRS will be used to determine effectiveness of treatment.

The HDRS17 will be used not only to determine eligibility, but also to collect additional data throughout the study. This questionnaire will also be administered on the 1st day of stimulation, the 5th day of stimulation, and the 2 and 4 week follow up, in addition to during the initial session.

The remainder of the assessments will collect data to monitor depressive symptoms throughout the study, as extra safety assessments. The BDI (*Attachment 1*) and CGI (*Attachment 3*) will be administered the 1st day of stimulation, the 5th day of stimulation, and at the 2 and 4 week follow ups. An EEG will be administered the 1st day of stimulation, the 5th day of stimulation and at the end of the 4 week follow up session. The EEG data will enable assessment of neurophysiological changes induced by stimulation.

14.4 Timing/Reports.

The stimulation adverse effects questionnaire will be administered at the end of each stimulation session. Any AE will be reported to the PI within 72 hours and medical monitor within 24 hours.

Reports will be run at the end of each week and any unusual activity that could be a cause of concern will be reported to the PI at weekly meetings.

14.5 Study Records Retention

According to the University of North Carolina at Chapel Hill's Archives and Record Management Services schedule for General Records Retention and Disposition Schedule 6.10, records will be kept for 5 years after the completion of the study or grant end date, whichever is later.

14.6 Protocol Deviations

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log (*Appendix O*) using the participant code as the identifier. This form will collect information such as the date the deviation occurred, details of what the deviation consisted of, any corrective and preventative actions that were taken as a result of the deviation, and the date that the PI and IRB were notified. The PI will review the information and initial once approved. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the participant's source document. Protocol deviations will be sent to the IRB per their guidelines. The site PI/study staff will be responsible for knowing and adhering to their IRB requirements.

15 PUBLICATION POLICY

This study will be registered on clinicaltrials.gov once IRB approved. There are no restrictions on publications since this is an investigator-initiated study funded by a grant agency (NARSAD) that has no influence on the publications resulting from this study. The aim is to publish the results of this study in a peer-reviewed, highly-ranked psychiatry journal.

16 LITERATURE REFERENCES

Ali, M.M., Sellers, K.K., and Frohlich, F. (2013). Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *J Neurosci* 33, 11262-11275.

Antal, A., Chaieb, L., Moliadze, V., Monte-Silva, K., Poreisz, C., Thirugnanasambandam, N., & ... Paulus, W. (2010). Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. *Brain Stimulation*, 3(4), 230-237. doi:10.1016/j.brs.2009.12.003

Beck, A. T., Steer, R. A., & Garbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, 8(1), 77-100. doi:10.1016/0272-7358(88)90050-5

Berlim, M.T., Van den Eynde, F., and Daskalakis, Z.J. (2013). Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Journal of psychiatric research* 47, 1-7.

Brunoni, A.R., Teng, C.T., Correa, C., Imamura, M., Brasil-Neto, J.P., Boechat, R., Rosa, M., Caramelli, P., Cohen, R., Del Porto, J.A., *et al.* (2010). Neuromodulation approaches for the treatment of major depression: challenges and recommendations from a working group meeting. *Arq Neuropsiquiatr* 68, 433-451.

Brunoni, A.R., Valiengo, L., Baccaro, A., Zanao, T.A., de Oliveira, J.F., Goulart, A., Boggio, P.S., Lotufo, P.A., Bensenor, I.M., and Fregni, F. (2013). The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry* 70, 383-391.

Dozois, D. A., Dobson, K. S., & Ahnberg, J. L. (1998). A psychometric evaluation of the Beck Depression Inventory–II. *Psychological Assessment*, 10(2), 83-89. doi:10.1037/1040-3590.10.2.83

Egan M.F., Kojima M., Callicott J.H., Goldberg T.E., Kolachana B.S., Bertolino A., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, 112(2), pp. 257–269. doi:10.1016/S0092-8674(03)00035-7

Frohlich, F., & McCormick, D. A. (2010). Endogenous electric fields may guide neocortical network activity. *Neuron*, 67(1), 129-43.

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., & Weinberger, D. R. (2003). Brain-Derived Neurotrophic Factor val⁶⁶ met Polymorphism Affects

Human Memory-Related Hippocampal Activity and Predicts Memory Performance. *The Journal Of Neuroscience*, 23(17), 6690-6694.

Henriques, J.B., and Davidson, R.J. (1990). Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. *J Abnorm Psychol* 99, 22-31.

Herrmann, C.S., Rach, S., Neuling, T., and Struber, D. (2013). Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front Hum Neurosci* 7, 279.

Kalu, U.G., Sexton, C.E., Loo, C.K., and Ebmeier, K.P. (2012). Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. *Psychol Med* 42, 1791-1800.

Khan, A., Khan, S. R., Shankles, E. B., & Polissar, N. L. (2002). Relative sensitivity of the Montgomery-Asberg Depression Rating Scale, the Hamilton Depression rating scale and the Clinical Global Impressions Rating Scale in antidepressant clinical trials. *International Clinical Psychopharmacology*, 17(6), 281-285. doi:10.1097/00004850-200211000-00003

Kleim, J. A., Chan, S., Pringle, E., Schallert, K., Procaccio, V., Jimenez, R., & Cramer, S. C. (2006). BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. *Nature Neuroscience*, 9(6), 735-737. doi:10.1038/nn1699

Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A., and Kleinschmidt, A. (2003). Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proc Natl Acad Sci U S A* 100, 11053-11058.

Leentjens, A. G., Verhey, F. J., Lousberg, R., Spitsbergen, H., & Wilmink, F. W. (2000). The validity of the Hamilton and Montgomery-Åsberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease. *International Journal Of Geriatric Psychiatry*, 15(7), 644-649. doi:10.1002/1099-1166(200007)15:7<644::AID-GPS167>3.0.CO;2-L

National Institute of Health. (2011). Further resources for NIH grantees. Retrieved from: http://grants.nih.gov/clinicaltrials_fdaaa/definitions.htm

Palva, S., and Palva, J.M. (2007). New vistas for alpha-frequency band oscillations. *Trends in neurosciences* 30, 150-158.

Pezawas L., Verchinski B.A., Mattay V.S., Callicott J.H., Kolachana B.S., Straub R.E., Egan M.F., Meyer-Lindenberg A, Weinberger D.R. (2004). "The Brain-Derived Neurotrophic Factor val66met Polymorphism and Variation in Human Cortical Morphology." *The Journal of Neuroscience* 24 (45): 10099–102. doi:10.1523/JNEUROSCI.2680-04.2004.

Sheehan, D. V., Lecrubier, Y., Sheehan, K., Amorim, P., Janavs, J., Weiller, E., & ... Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I): The development and

validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal Of Clinical Psychiatry*, 59(Suppl 20), 22-33.

Williams, J. W. (2001). Standardizing the Hamilton Depression Rating Scale: past, present, and future. *European Archives Of Psychiatry And Clinical Neuroscience*, 251(Supl2), 6-12.
doi:10.1007/BF03035120

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *The British Journal Of Psychiatry*, 133429-435.
doi:10.1192/bjp.133.5.429

SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

A detailed schematic describing all visits and assessments.

Procedures	Initial Session	Day 1 of Stimulation	MDD Study Outline			
			Days 2 –4 of Stimulation	Day 5 of Stimulation	Week 2 Follow Up	Week 4 Follow Up
Signed Consent Form	X					
Assessment of Eligibility Criteria	X					
Demographics	X					
Medications	X					
BDNF test	X					
MINI	X					
HDRS	X	X		X	X	X
YMRS		X	X	X	X	X
Suicide Assessment		X	X	X	X	X
MADRS		X		X	X	X
BDI		X		X	X	X
CGI		X		X	X	X
MOCA		X				X
<i>n</i> -back working memory		X		X		X
Stimulation		X	X	X		
EEG	X	X		X		X
Stimulation Adverse Events Questionnaire		X	X	X		X

APPENDIX B: STUDY START UP CHECKLIST

Study Start Up Checklist

Study Title: _____

Funding Source: _____

Date Completed	
CRMS Recorded Created	_____
IRB Application Submitted	_____
	Approved Date : _____
CVs/Certifications/Medical License	_____
IRB Roster	_____
IRB Statement of Compliance	_____
PI Signature of Protocol	_____
HD-974 Forms	_____
Date Completed	
Study Binders Created	_____
Regulatory Documents Filed	_____
Protocol Deviation Tracking Log Filed	_____
Completion of Site Training, Filed	_____
Delegation Log Completed	_____
Develop Recruitment Plan	_____
Begin Pre-Screening	_____
Source Documents Created	_____
Participant Folders Created	_____

Schedule Study Start Up Meeting	_____
Lab Kits Received	_____
Participant Supplies Received	_____
Investigational Device Received	_____

APPENDIX C: DOCUMENTATION OF INFORMED CONSENT PROCESS

Abbreviated Study Title: _____

Participant Name: _____ Date of Birth: _____

Medical Record #: _____

Please **INITIAL** next to “**Yes**” or “**No**” by each line as appropriate (**if “No,” an explanation MUST be provided in the notes section below**).

____ Yes ____ No Participant and/or the participant’s legally authorized representative (LAR) was given a copy of the consent document to read.

____ Yes ____ No Ample time was provided for reading the consent document, and the participant (or participant’s LAR) was encouraged to ask questions.

____ Yes ____ No All questions and concerns were addressed to the satisfaction of the participant (or participant’s LAR) prior to signing the consent document.

____ Yes ____ No The PI or CO-I was available for questions prior to the subject signing the consent.

____ Yes ____ No The subject (or subject’s LAR) agreed to participate in the study and signed/dated the consent document.

____ Yes ____ No A copy of the signed consent document was provided to the participant (or participant’s LAR).

☐ Verbal consent was obtained (per IRB approved consent process).

Documentation of the process and the individual(s) witnessing the process is described below.

____ Yes ____ No No procedures specifically related to the study were performed prior to the participant signing the consent document.

The details of this research study were discussed with the participant (or participant’s LAR), including an explanation of all of the elements of the consent document. The IRB-approved consent document was signed and dated by the participant (or participant’s LAR) and a copy of the signed consent document was placed in the participant’s medical record (unless otherwise noted). No activities specifically related to the research were initiated until after the execution of the consent document. The principal investigator was notified of the participant’s consent to be enrolled in the study and agrees with enrollment of subject.

The participant (or participant’s LAR) signed consent document version _____ on

_____ (date) at _____ (time).

Notes: _____

Signature of Person Obtaining Consent

Date

Time

APPENDIX D: CONSENT AMENDMENT TRACKING LOG

Study Title:

Change Initiated by:		Adjustments made to consent form	Date Submitted to IRB	Date of IRB Answer	Requires Stipulations? (Y/N)	Stipulation Submission Date	IRB Approval Date
Initials	Reference ID						

APPENDIX E: INFORMED CONSENT EVALUATION FEEDBACK

Name of Research Study:

.....

You have been asked to be in a research study. This sheet will help you think of questions to ask but you may have other questions. This is not a test. We want to be sure you understand what it means to be in this research study. You should understand the research before you decide whether or not to participate.

1. What is the *purpose* of the research?
2. What are the possible *benefits* of the research?
3. What are the possible *risks* of the research?
4. Will everyone receive the *same* treatment?
5. How is this research different than the care or treatment I would get if I wasn't in the research study?
6. Does in the research cost me anything extra?
7. Can you stop being in the research once you've started?
8. Who will view your *medical* records?
9. Who do you call if I have questions about being a research subject?
10. Any questions?

APPENDIX F: IRB AMMENDMENT TRACKING LOG

Study Title:

Change Initiated by:		Description of IRB: Type and Brief Summary	Date Submitted to IRB	Date of IRB Answer	Requires Stipulations? (Y/N)	Requires Updated Consent Form? (Y/N)	Stipulation Submission Date	IRB Approval Date
Initials	Reference ID							

APPENDIX G: NOTE TO FILE

IRB#: 14-1622

PI: Flavio Frohlich

Study Title:

Date of Occurrence: _____

Research Name: _____

Participant ID: _____

Reason for Note:

Note:

Corrective action (if applicable):

Signature: _____

Date: _____

APPENDIX H: INCLUSION/EXCLUSION CRITERIA CHECKLIST (WITH PI SIGNATURE FOR PARTICIPANT ELIGIBILITY)

Participant ID: _____

Date: _____

Inclusion Criteria		
Ages 18-65 years	Yes	No
DSM-IV diagnosis of MDD; unipolar, non-psychotic	Yes	No
Hamilton Rating Depression Rating Scale score >8	Yes	No
Low suicide risk	Yes	No

Exclusion Criteria		
DSM-IV diagnosis of alcohol or substance abuse (other than nicotine) within the last month or a DSM-IV diagnosis of alcohol or substance dependence (other than nicotine) within the last 6 months	Yes	No
Medical or neurological illness (unstable cardiac disease, AIDS, malignancy, liver or renal impairment) or treatment for a medical disorder that could interfere with study participation	Yes	No
History of traumatic brain injury, reoccurring seizures or later cognitive rehabilitation or causing cognitive sequelae	Yes	No
Prior brain surgery	Yes	No
Any brain devices/implants, including cochlear implants and aneurysm clips	Yes	No
Co-morbid neurological condition (i.e. seizure disorder, brain tumor)	Yes	No
Non English speakers	Yes	No
Pregnancy, nursing, or if female and fertile, unwilling to use appropriate birth control measures during study participation	Yes	No
Capacity to understand all relevant risks and potential benefits of the study (informed consent)	Yes	No
Current axis I mood, psychotic disorder other than MDD		
Lifetime comorbid psychiatric bipolar or psychotic disorder		
Eating disorder (current or with the past 6 months)		
Obsessive-compulsive disorder (lifetime)		
PTSD (current or with the past 6 months)		
ADHD (current or with the past 6 months)		
Current use of benzodiazepines and/or antiepileptic drugs		

If the responses to all the inclusion criteria are YES and all the exclusion criteria are NO, the participant is able to participate in the trial.

Is the participant eligible to participate in the trial?

YES

NO

If NO, discontinue subject.

If YES, I have reviewed the inclusion and exclusion criteria and have determined that the participant is eligible for participation in the trial.

Investigator Signature: _____

Date: _____

APPENDIX I: TELEPHONE CONTACT LOG

Protocol Title: _____

Subject #: _____

Date/Time	Incoming/Outgoing	Message/Conversation	Reason for calling	Comments/Researcher Initials
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		
	Incoming Outgoing	Message Conversation		

APPENDIX J: ADVERSE EVENTS TRACKING LOG

Participant ID	√ if AE meets definition of serious*	Was this an Expected or Unexpected Event?	Grade / Intensity 1. Asymptomatic 2. Mild 3. Moderate 4. Severe	Date of Incident	Relationship to study device 1. Related 2. Possibly 3. Not Likely 4. Not Related	Was Action Taken?	Action(s) Taken:	Outcome: 1. Recovered 2. Not Recovered 3. Recovered w/Sequel 4. Fatal 5. Unknown	PI Initials / Date
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			
		Expected/ Unexpected				Yes / No			

APPENDIX K: UNEXPECTED/SERIOUSADVERSE EVENT TRACKING LOG

Participant ID	Date Event Occurred	Was this an Expected or Unexpected Event?	Date Study Team Notified of Event	Event	Date Reported to IRB	Study SAE Form Completed
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
		Expected/ Unexpected				<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

APPENDIX L: ADVERSE EVENT REPORT FORM

Adverse Effects Report:

Reasons for Report (adverse event, time, date and place of occurrence if available):

1. What do we already know about the therapy?
a)
2. What is the temporal relationship of the AE to the study therapy?
a)
3. Does the AE improve or disappear when the therapy is stopped?
a)
4. Is the AE a worsening of baseline symptom(s)?
a)
5. Is the AE a result of an underlying concurrent medical condition(s) or concurrent medication(s)?
a)
6. Additional Information provided by research team
a)

Research team member signature _____

Date _____

Co-Investigator:

Steps to be taken (if applicable)

CI signature

Date _____

PI Comments:

Steps to be taken (if applicable)

PI signature

Date

APPENDIX M: SERIOUS ADVERSE EVENT REPORT FORM

Serious Adverse Event Form

Participant ID: _____

1. Location of SAE (e.g., clinic, home): _____
2. Age: _____
3. Gender: Male Female
4. SAE term (provide diagnosis): _____
- 4a. If diagnosis is not known, symptoms: _____
5. Date of onset: _____ (dd/mm/yyyy)
6. What is the severity grade of the serious adverse event?

- ☐ Grade 1: Mild
- ☐ Grade 2: Moderate
- ☐ Grade 3: Severe
- ☐ Grade 4: Life-threatening
- ☐ Grade 5: Death

7. Did the participant receive the investigational product or study intervention prior to this SAE?
- ☐ Yes ☐ No ☐ N/A

- 7a. If yes, identify the investigational product or study intervention received prior to the SAE:
Investigational Product/Study Intervention

Dose _____
Units _____
Frequency _____

Start Date ____/____/____ (dd/mm/yyyy)
Stop Date ____/____/____ (dd/mm/yyyy)
Check if Ongoing ☐

8. Action taken with investigational product/study intervention:

- ☐ Continued
- ☐ Lowered
- ☐ Interrupted
- ☐ Discontinued
- ☐ Increased
- ☐ N/A

9. Outcome of SAE:

- ☐ Ongoing at this time
- ☐ Resolved without sequelae
- ☐ Resolved with sequelae
- ☐ Death
- ☐ Present at death, not contributing to death

10. Date of resolution: _____ (dd/mm/yyyy) or
☐ Ongoing at end of study

11. Seriousness criteria? (Check all that apply)

- ☐ Life-threatening
- ☐ Required hospitalization or
- ☐ Prolongation of existing hospitalization
- ☐ Congenital anomaly
- ☐ Disabling/incapacitating
- ☐ Important medical event
- ☐ Fatal

If fatal: 11a. Date of death: _____ (dd/mm/yyyy)

11b. Primary cause of death: _____

11c. Was an autopsy performed?

- ☐ Yes
- ☐ No

12. Relationship to investigational product/study intervention:

- ☐ Related (Associated with the use of the study intervention. There is a reasonable possibility that the experience may have been caused by the study intervention.)
- ☐ Unrelated

13. If SAE is unrelated to investigational product/safety intervention, select all possible etiologies:
Concurrent illness, disease, or other external factors, specify:

Concurrent medication, specify:

Secondary study procedure, specify:

Accident, trauma, or other external factors, specify:

Other, specify:

14. Did the participant receive any relevant concomitant medications in response to the SAE?

- ☐ Yes
- ☐ No

14a. If yes, please specify: Name, Start and Stop date or On going

15. Did the participant receive any treatments/procedures in response to the SAE?

☐ Yes
☐ No

15a. If yes, please specify

16. Did the participant receive relevant laboratory or diagnostic tests in response to the SAE?

Yes
No

16a. If yes, provide the name of the test and results with normal ranges and/or supplemental exams below:

17. Narrative/Comments (provide a description of the serious adverse event including chronological clinical presentation and evolution of the serious adverse event and associated signs/symptoms):

This image shows a blank sheet of white paper with horizontal ruling lines. The lines are evenly spaced and extend across the width of the page. There are no margins, text, or other markings on the paper.

18. Completion of form: printed names, signatures and date of signature

Person Completing Form
(print name)

Person Completing Form
(signature)

Date

Investigator (print name)

Investigator (signature)

Date

APPENDIX N: DELEGATION OF AUTHORITY

	USE ONE VERTICAL COLUMN FOR EACH DESIGNEE														
Designee (full name)	Courtney Lugo	Juliann Mellin	Dr. Asa Cordle	Michael Boyle	Dr. David Rubinow	Dr. Flavio Frohlich									
Title & Position															
Delegated Activity (see codes)															
Designee Signature & Dates															
Designee Initials (signed)															
	<p>Activity Codes:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">01: Informed Consent</td> <td style="width: 33%;">04: CRF Entries</td> <td style="width: 33%;">07: Data Entry</td> </tr> <tr> <td>02: Initial Session Review for Eligibility</td> <td>05: Device Administration</td> <td>08: Adverse Event Assessment</td> </tr> <tr> <td>03: Questionnaire Administration</td> <td>06: EEG Administration</td> <td>09: Adverse Event</td> </tr> </table> <p>Documentation/Reporting</p> <p>10: Medical Monitor</p>						01: Informed Consent	04: CRF Entries	07: Data Entry	02: Initial Session Review for Eligibility	05: Device Administration	08: Adverse Event Assessment	03: Questionnaire Administration	06: EEG Administration	09: Adverse Event
01: Informed Consent	04: CRF Entries	07: Data Entry													
02: Initial Session Review for Eligibility	05: Device Administration	08: Adverse Event Assessment													
03: Questionnaire Administration	06: EEG Administration	09: Adverse Event													
	<p>Investigator's Authorization: I hereby delegate the above significant research-related duties to the following persons and understand that the overall responsibility for conduct of the research remains with me.</p> <p>¹Investigator's Signature: _____ Date: _____</p>														

APPENDIX O: PROTOCOL DEVIATION LOG

Participant ID	Date Occurred	Description	CAPA*	Date PI Notified	Date IRB Notified	PI Initial/Date

APPENDIX P: ENROLLMENT LOG

Subject ID		Date Consent Signed	Gender	Race	Ethnicity	Treatment Arm / Group	Explanation if subject did not complete study / Comment
1			M <input type="checkbox"/> F <input type="checkbox"/>				
2			M <input type="checkbox"/> F <input type="checkbox"/>				
3			M <input type="checkbox"/> F <input type="checkbox"/>				
4			M <input type="checkbox"/> F <input type="checkbox"/>				
5			M <input type="checkbox"/> F <input type="checkbox"/>				
6			M <input type="checkbox"/> F <input type="checkbox"/>				
7			M <input type="checkbox"/> F <input type="checkbox"/>				
8			M <input type="checkbox"/> F <input type="checkbox"/>				
9			M <input type="checkbox"/> F <input type="checkbox"/>				
10			M <input type="checkbox"/> F <input type="checkbox"/>				
11			M <input type="checkbox"/> F <input type="checkbox"/>				
12			M <input type="checkbox"/> F <input type="checkbox"/>				
13			M <input type="checkbox"/> F <input type="checkbox"/>				
14			M <input type="checkbox"/> F <input type="checkbox"/>				
15			M <input type="checkbox"/> F <input type="checkbox"/>				

APPENDIX Q: TRAINING LOG

Title of Training: _____

(e.g., Protocol; Amendment; IRB [include version #/date])

DATE: _____

By signing below, each staff member verifies they have been trained on the information and understand the

Training Date (if different than above)	Trainee Name (please print)	Trainee Signature	Training Format (ie Presentation; Self-Study)

obligations/responsibilities associated with this training.

Trainer Name (if relevant): _____

(Please print)

Trainer Signature (if relevant): _____

APPENDIX R: PARTICIPANT OFF STUDY FORM

Participant Initials

ID

Date:

Month

Day

Year

Participant Off Study

Date participant went Off Study:

Month

Day

Year

INDICATE OFF STUDY REASON:

- ☐ Study Activities Completed
- ☐ Side effects of study intervention (complete applicable SAE form or AE Tracking Log)
- ☐ Death
- ☐ Participant lost to follow-up* (provide comments below)
- ☐ Participant refused follow-up* (provide comments below)
- ☐ Other* (provide comments below)
- ☐ Participant withdrew (complete Early Withdrawal section below)

Was treatment unblinded? ☐¹ Yes ☐² No ☐³ Not Applicable

Early Withdrawal

Last Visit Completed:

☐ Early Withdrawal form not completed

- ☐ Screening Visit
- ☐ Visit 1
- ☐ Visit 2

- ☐ Visit 3
- ☐ Visit 4
- ☐ Visit 5

- ☐ Visit 6
- ☐ Visit 7

Indicate the **primary** reason the participant has withdrawn from the study (select only one):

- ☐ Participant deemed eligible but declined participation
- ☐ Participant deemed inappropriate for study participation by the PI
- ☐ Participant was determined to be ineligible after enrollment* (provide comments below)
- ☐ Identification of disease/condition after enrollment that warrants withdrawal*
- ☐ Unable to continue due to personal constraints*
- ☐ Side effects of study intervention * (complete UWI-02-007 Adverse Event Tracking Log)
- ☐ Other *

*Additional explanation required:

FORM COMPLETED BY: _____

APPENDIX S: TELEPHONE RECRUITMENT SCRIPT

Hello, my name is _____. Are you contacting me in regards to the non-invasive brain stimulation study?

If 'No', redirect them as necessary)

(If 'Yes', proceed)

Do you have time now to hear about the study, answer a few screening questions, and schedule your first visit?

(If 'No', ask for a good time to call back)

(If 'Yes', proceed)

Great! This study is looking at abnormal rhythms of brain activity in Major Depressive Disorder (and how they) respond to very weak applied electric currents. Findings from this study will help the development of treatments for the symptoms of depression. In the study, a very weak electric current will be applied to your scalp. Some people report a mild tingling because of this stimulation, but no other side effects have been found. It is not a shock and should cause no pain.

Participation in this study includes one to eight sessions, with one session being an initial information session, then 5 stimulation sessions, followed by a 2 and 4 week follow up session. The stimulation sessions need to be over a consecutive week. You will be compensated for each hour of your time spent participating in the study, with a \$20 completion bonus for finishing the study. Therefore, the maximum compensation for this study is \$280 for completing all of the sessions. Are you still interested in participating?

(If 'No', thank them for their time)

(If 'Yes', proceed)

Great! In order to make sure you're eligible for the study, I need to ask you a few questions. Please answer yes or no. You do not need to provide any further details.

(If the answer given is not the same as the answer shown, thank the individual for his or her interest and say unfortunately, they do not qualify for the current study)

- Are you 18 years old or older? (Yes)
- Have you ever, or are you currently being treated for a neurological condition (i.e. epilepsy, migraines, etc)? (No)
- Are you currently taking medication for the treatment of depression or any other psychiatric illness? (No)
 - Have you ever taken medication for a mood disorder?
 - If yes, has it been at least 6 months since then?
- How long have you been depressed?
- What steps have you taken to treat this depression?

- Have you ever had brain surgery? (No)
- Do you have any brain devices or implants, including a cochlear implant or aneurysm clip? (No)
- Have you ever been diagnosed with a traumatic brain injury? (No)
- For females only, is there a chance you may be pregnant? (No)

Follow-up Questions

- Have you been diagnosed with Major Depressive Disorder by a professional (i.e. a psychiatrist or other licensed clinician)?
- Have you ever been hospitalized?
 - If yes, was it in anyway related to a mood disorder or psychiatric condition?
 - If yes, when did this occur?
- Do you wear glasses/contact lenses?
 - Could you bring your contact lenses for the study visits instead of wearing your glasses?

(If answered according to all indicated responses, continue)

You are eligible for participation in the first session of the study. At the first session we will determine your eligibility for the remainder of the sessions. I'd like to schedule your first session now. It will last approximately 3 hours. All testing will be conducted at either UNC Hospital or the NCPRC in Raleigh. (Specify time).

(Schedule a time for first session)

I will send you an email or letter by mail, depending on your preference, confirming this time, and providing directions on how to find the specific location of you session. We will also send you an email, if you chose this form of communication to confirm your appointment 24 hours beforehand. Please respond to this email so we know you are still coming. If you have any questions before then, please don't hesitate to contact us at this phone number or at Courtney_lugo@med.unc.edu

Thank you for your time.